

REMARKS

Withdrawal of the final rejection, favorable reconsideration and allowance of the present application based on the enclosed documents and the following remarks are respectfully requested.

Upon entry of the above amendments, claims 15-20 will be pending. Applicants reserve the right to continue prosecution of the subject matters of cancelled claims 21-25 and any other disclosed but not claimed subject matter.

The amendments to claims 15 and 19 merely incorporate the test procedures previously identified by reference to the test procedures described in the specification on page 10 of the specification. No change in scope or meaning is intended or accomplished. Accordingly, the amendments do not raise an issue of new matter and do not raise any new issue for consideration or search. Therefore, since the amendments overcome the formal objection b) on page 4 of the Office action, entry of the amendment is requested.

The items raised in the Detailed Action will be considered in the same order as presented.

The acknowledgment of the filing of the priority documents is appreciated.

A new IDS/Form PTO-1449, with partial translation of the Japanese publication previously filed on, or intended to be filed, January 22, 2002 is enclosed for the Examiner's convenience.

The defect in the oath/declaration is noted. However, that the address of inventor B. Rankin was changed after the Declaration was executed. Accordingly, a new oath/declaration will be obtained and filed as soon as possible.

A new drawing sheet for Fig. 1 is attached, along with a letter to the Draftsman requesting approval and entry in this application. The modified Fig. 1, shows the overlapping lines for Ca:Fe 3:1 aged and unaged by following the Examiner's suggestion to show the overlapping data points by using a shape ("X") for the unaged product that distinguishes from the shape ("■") used to represent the data points for the aged product.

The objection to claim 16 as failing to comply with 37 CFR 1.75(d) is noted. However, as previously explained, claim 16 is more specific than and does further limit the subject matter of claim 15 from which it depends.

It is specifically noted that the pH range in claims 15 (3 to 7) is broader than the pH range (2 to 8) recited in claim 16.

The requirement of Claim 15 is that the material has a certain phosphorous binding capacity throughout the range of pH values from 3 to 7. Hence, a compound which falls within this claim could have a phosphorus binding capacity of less than 30% at a pH of 2-3 or 7-8. However, the requirement in Claim 16 is that the compound has the 30% binding capacity over the full range 2 to 8 (i.e. 2-3 + 3-7 + 7-8). This is more limiting, because it must be assumed that fewer compounds can meet this more stringent requirement.

Accordingly, this basis for objection should be withdrawn.

The rejections of claims 22, 24 and 25, as anticipated by, or as unpatentably obvious over, U.S. 5,173,284 is moot in view of the cancellation of these claims which has been done solely for the purpose of expediting prosecution by reducing the issues for appeal. However, it is specifically noted that Applicants do not agree with this rejection and reserve the right to separately prosecute this subject matter.

Claims 15-25 are rejected as being obvious, within the meaning of 35 USC 103(a), over JP 5-155,776 in view of German Patent 34 02 878 to Dietl. This rejection is respectfully traversed for at least the following reasons.

As noted above, a partial English translation of JP 5-155,776 is enclosed.

As understand the position of the Examiner is that performing the precipitation described in JP 05 155 776 in the presence of, say, calcium sulphate (which is mentioned in DE 3 402 878) will produce a compound within the scope of the rejected claims. Applicants respectfully disagree.

First the wording of Claim 1 refers to “[a] solid mixed metal compound” meaning that a single compound is claimed albeit that this compound is based on more than one metal. The compound produced using the technique postulated by the Examiner will give an iron compound mixed with a calcium compound. Therefore, two compounds would be present and neither would be based on more than one metal. Furthermore, Claim 1 says that the compound is “obtained as a precipitate from a solution of a mixture of metallic salts.” In the process suggested by the Examiner the calcium sulphate is a solid which is pre-formed (i.e. not obtained as a precipitate together with the iron compound) and there is no solution of a mixture of metallic salts; there would be a solution of iron salt containing some solid calcium sulphate. Hence, what the Examiner suggests is obvious is not the subject matter defined in the pending and rejected claims.

It is, of course, an extremely fundamental point in chemistry, namely the difference between a compound (which is claimed) and a mixture (which is what the Examiner postulates is obvious). A simple example is a mixture of iron fillings and sulphur. Such a mixture has the combined properties of the components. For example, reaction with an acid will produce hydrogen. However, iron and sulphur can be reacted to form iron sulphide, which is a compound, not a mixture and this compound has properties which are distinct from the properties of its "component parts." For example, reaction with an acid produces hydrogen sulphide.

Another and important characteristic of the claimed mixed metal compound as recited in the embodiment of Claim 1 is that it has a specified phosphate absorption "over a pH range of 3 to 7." The products which are claimed have the specified 30% binding capacity over the whole of this range, not just at any point within the range.

For at least these reasons, it is again submitted that the combination of JP 05 155 776 and DE 3 402 878 does not lead to the compound of the rejected claims. At most, the disclosure leads not to one compound, but to a mixture of compounds. Such a mixture will have the properties of the components.

Again, this may be readily appreciated from Figure 3 of JP 05 155 776. This figure demonstrates a maximum binding of about 30%, but only in the range 2 to 3. For the range 4 to 8 the binding capacity is not more than 10%. As stated above, the present claims recite that the binding capacity of at least 30% by weight is present over the entire range of 3 to 7, or even more, over the entire range of 2 to 8, not just over the range of 2 to 3.

DE 3 402 878 presents results on several calcium compounds on page 12. The best appears to be calcium sulphate dihydrate with a binding capacity of 280 to 300 mg/g over a pH range of 7.0 to 8.0. Note, also, the aluminum hydroxide content between 10 and 20% at pH values in this range. This suggests that the calcium sulphate dihydrate of DE 3 402 878 would have a binding capacity of 35% at most (i.e. 20% x 300/170). However, from Figure 3 of JP 05 155 776 it is known that the iron compound therein has a binding capacity of about 5 to 8% at pH 7 to 8. Therefore, a mixture of the compounds of JP 05 155 776 and DE 3 402 878 must have a phosphate binding capacity below 30% in the pH range 7 to 8 for all mixtures except, perhaps, for those containing a high proportion of calcium salt.

Accordingly, it must be concluded that, on the evidence disclosed in the two references, the mixture would not have a phosphate binding capacity as defined, over the

range of pH values. Consequently, it is respectfully submitted that the Examiner has not established a *prima facie* case that the invention is obvious because the combination does not lead to the compound as claimed, either by chemical composition or in its performance.

For completeness, the following discussion specifically addresses the Examiner's rebuttals of the arguments presented on January 22, 2002.

a) The distinction between a compound and a mixture is certainly well understood. It is improper to ignore the claim recitation of "compound." It is again submitted that the result of inclusion CaSO₄ etc. in the JP 05 155 776 process leads, at most, to a composition not within the pending and rejected claims. The reference to "hydrotalcite" was, perhaps misleading, but in any event was intended only to serve as an illustration of the kind of compound being claimed, not to the actual scope of the claimed invention.

(b) The Examiner argues that the addition of CaSO₄ etc. "is expected to synergistically enhance effectiveness" is not understood. Certainly, assuming "synergism" is contrary to one of the basic tenets used in patent law to assess an unexpected effect. Surely, what is expected from a mixture of two compounds is that the mixture will have properties which are an additive combination of the properties of the components. If synergism is perceived, the effect is greater than the combined effects. Normally, the discover of a synergistic effect in a mixture will be considered to be an unexpected effect and hence would negate a *prima facie* finding of obviousness.

Applicants have invented a compound which is better than a mixture of the elements present therein and better than that of the individual compounds used in its preparation, however, it would not be necessary to refer to this as "a synergistic effect" because it is a property of the compound, not an unexpected property of a mixture.

(c) This argument has been addressed above. The pending and rejected claims certainly do cover pH values as low as 2, but in all cases the 30% performance occurs over the full range of 3 to 7 or 2 to 8. The point at issue is that the JP 05 155 776 only fulfills the 30% criterion for a limited part of this range. Further, as the explanations above demonstrate, the references show a phosphate binding capacity below 30% for at least a substantial part of the range. The information which may be gleaned from the references suggests a value below 30%.

(d) The Examiner seems to have misunderstood the argument regarding solubility. It is true that the calcium compounds of DE 3 402 878 are described therein as "poorly soluble"

and poor solubility is mentioned in the specification at page 1, line 28. However this is just a way of describing the compounds. It is not relevant to the performance of the products. The statement at page 2, lines 1 to 4, is that calcium compounds are known in the art to be rather poor for phosphate removal. JP 05 155 776 demonstrates that the iron compounds disclosed therein are also poor phosphate binders, at least at a pH above about 3. Therefore, a skilled person would not be motivated to combine them because all that would be expected is a rather poor phosphate binder. In addition, of course, as previously argued, the combination suggested by the Examiner does not lead to the claimed compound; it would only give a mixture.

(e) Section 2145 (II) in the MPEP relates to the recognition of latent properties in the prior art. This is not the case here. The phosphate binding capacity is not a property unrecognized in the prior art; it is reported therein and a skilled person has it available. Hence, it seems that this section is not relevant to the arguments presented. Once again, unlike the mixtures described/suggested in the prior art Applicants have made a class of new compounds, not a mixture of the compounds disclosed in the references.

(f) It is asserted that there is no evidence that a mixture of compounds is formed if one combines the teachings of JP 05 155 776 and DE 3 402 878. It is respectfully submitted that the evidence is available from the documents and elementary chemistry. The preparation of the product of JP 05 155 776 (paragraph 20) states that the gel precipitate is formed at pH 7. DE 3 402 878 teaches the use of compounds which are “poorly soluble” at pH 6-9 (first line of abstract). Hence, the suggested procedure involves the precipitation of an iron compound in the presence of a solid, insoluble calcium or magnesium compound. The only logical outcome would be a mixture of a calcium compound and an iron compound. Moreover, this is not a compound which is obtained from “a solution of a mixture of metallic salts.”

It is accepted that FeCl_3 (a precursor in the JP 05 155 776 preparation) is in solution, but because the calcium compound is “poorly soluble,” it is not present in solution. Hence, whatever is formed using the method suggested by the references, must be distinct from what is claimed herein, which, in part, is defined by its method of preparation.

As to the question of predictability (i.e. what a skilled person would expect by combining JP 05 155 776 and DE 3 402 878), there is simply no evidence from which the practitioner would expect to arrive at the present invention based on the prior art disclosures. Section 2143 in the MPEP, which is quoted by the Examiner, says that prior art can be

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combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. The point overlooked by the Examiner is that the evidence that is present in the prior art is that there is no reasonable expectation of success, because the predicted phosphate binding capacity would be below 30%. In fact, there is a reasonable expectation of failure.

In addition, the statements at page 1, line 27 to page 2, line 4, which are consistent with the disclosures of DE 3 402 878, were written in 1997 and reflect clinical experience at that date. At the date of Applicants' invention, a skilled person would be aware of this knowledge in the art, as well as the disclosures of DE 3 402 878, and this knowledge would also help to assess the expectation of success or failure. No reasonable expectation of success can be identified based on the teachings of the cited references.

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned "Version with markings to show changes made".

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All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

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Enclosures: Appendix
Information Disclosure Statement
Drawing Cover Sheet with Figure 1

Date: September 24, 2002
Attorney Reference: 081935/0266300

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APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

15. (Twice amended) A solid mixed metal compound, having phosphate binding capacity, and useful as a medicament, comprising the compound obtained as a precipitate from a solution of a mixture of metallic salts, free from aluminum, and containing (i) hydroxyl and/or carbonate ions; (ii) sulphate, chloride, oxide, or mixtures thereof; (iii) iron (III) and (iv) at least one additional metal selected from the group consisting of magnesium, calcium, lanthanum and cerium, said compound having a phosphate binding capacity of at least 30%, as measured by any of the following test methods (1), (2) or (3), over a pH range of from 3 to 7;

- (1) adding 1 gram of said solid mixed metal compound to 25 ml of 40 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature of 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (2) adding 1 gram of said solid mixed metal compound to 25 ml of 20 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature for 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (3) mixing 250 ml milk, 50 g cornflakes, 2 slices bread and 5 mg marmite in a stomacher containing 0.01 M HCl for 30 minutes, removing a 20 ml aliquot and measuring the phosphate content of a supernatant obtained from said aliquot, adding 2 g of said solid mixed metal compound to the contents of the stomacher, mixing for a further 30 minutes, taking another aliquot of food and measuring the phosphate content of a supernatant obtained from this aliquot.

19. (Twice Amended) A solid mixed metal compound having phosphate binding capacity, and useful as a medicament, comprising a hydroxy carbonate containing iron (III) and magnesium metals, further containing sulphate, chloride, oxide or mixtures thereof and

free from aluminum, and having a phosphate binding capacity of at least 30% by weight, as measured by any of the test methods 1, 2 or 3, over a pH range of 2 to 8;

- (1) adding 1 gram of said solid mixed metal compound to 25 ml of 40 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature of 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (2) adding 1 gram of said solid mixed metal compound to 25 ml of 20 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature for 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (3) mixing 250 ml milk, 50 g cornflakes, 2 slices bread and 5 mg marmite in a stomacher containing 0.01 M HCl for 30 minutes, removing a 20 ml aliquot and measuring the phosphate content of a supernatant obtained from said aliquot, adding 2 g of said solid mixed metal compound to the contents of the stomacher, mixing for a further 30 minutes, taking another aliquot of food and measuring the phosphate content of a supernatant obtained from this aliquot.

20. (Amended) A method for treating hyperphosphataemia, in an animal in need thereof, which comprises administering to said animal, a therapeutically effective amount of a [the] solid mixed metal compound [of any one of claims 15, 16 or 19] having phosphate binding capacity, and comprising the compound obtained as a precipitate from a solution of a mixture of metallic salts, free from aluminum, and containing iron (III) and at least one additional metal selected from the group consisting of magnesium, calcium, lanthanum and cerium, said compound having a phosphate binding capacity of at least 30%, as measured by any of the following test methods (1), (2) or (3), over a pH range of from 3 to 7;

- (1) adding 1 gram of said solid mixed metal compound to 25 ml of 40 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature of 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;

- (2) adding 1 gram of said solid mixed metal compound to 25 ml of 20 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature for 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (3) mixing 250 ml milk, 50 g cornflakes, 2 slices bread and 5 mg marmite in a stomacher containing 0.01 M HCl for 30 minutes, removing a 20 ml aliquot and measuring the phosphate content of a supernatant obtained from said aliquot, adding 2 g of said solid mixed metal compound to the contents of the stomacher, mixing for a further 30 minutes, taking another aliquot of food and measuring the phosphate content of a supernatant obtained from this aliquot.

Claims 16, 17, and 18 are cancelled. Claims 26-32 are added.

End of Appendix

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Page 4, delete the whole paragraph starting in line 22, and replace it with the following new paragraph:

-- Fig. 1 shows the effect of pH and ageing on percentage phosphate binding of mixed metal compounds. In Fig. 1,

| | | | |
|---------------------|----------|-----|---------------|
| ○ | Mg:Fe | 3:1 | prep 2 unaged |
| ● | Mg:Fe | 3:1 | prep 2 aged |
| △ | Mg:Fe | 2:1 | prep 1 unaged |
| ▲ | Mg:Fe | 2:1 | prep 1 aged |
| -- ☒ [□] | Ca:Fe | 3:1 | unaged |
| ■ | Ca:Fe | 3:1 | aged |
| ★ | Ca:Fe:Mg | | unaged |
| ★ | Ca:Fe:Mg | | aged |

IN THE CLAIMS

--15. (Amended) A solid mixed metal compound, having phosphate binding capacity, and useful as a medicament, comprising the compound obtained as a precipitate from a solution of a mixture of metallic salts, free from aluminum, and containing iron (III) and at least one additional metal selected from the group consisting of magnesium, calcium, lanthanum and cerium, said compound having a phosphate binding capacity of at least 30%, as measured by any of the following test methods (1), (2) or (3) [1, 2 or 3, as described in the specification], over a pH range of from 3 to 7;

(1) adding 1 gram of said solid mixed metal compound to 25 ml of 40 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature of 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;

- (2) adding 1 gram of said solid mixed metal compound to 25 ml of 20 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature for 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (3) mixing 250 ml milk, 50 g cornflakes, 2 slices bread and 5 mg marmite in a stomacher containing 0.01 M HCl for 30 minutes, removing a 20 ml aliquot and measuring the phosphate content of a supernatant obtained from said aliquot, adding 2 g of said solid mixed metal compound to the contents of the stomacher, mixing for a further 30 minutes, taking another aliquot of food and measuring the phosphate content of a supernatant obtained from this aliquot.

19. (Amended) A solid mixed metal compound having phosphate binding capacity, and useful as a medicament, comprising a hydroxy carbonate containing iron (III) and magnesium metals, free from aluminum, and having a phosphate binding capacity of at least 30% by weight, as measured by any of the test methods (1), (2) or (3) [1, 2 or 3, as described in the specification,] over a pH range of 2 to 8;

- (1) adding 1 gram of said solid mixed metal compound to 25 ml of 40 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature of 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (2) adding 1 gram of said solid mixed metal compound to 25 ml of 20 mmol l⁻¹ sodium phosphate buffer solution, homogenizing and gently agitating at room temperature for 30 minutes, centrifuging at 3000 rpm for 5 minutes, filtering through 0.22 µm millipore filter and measuring the soluble phosphate in the supernatant thus produced;
- (3) mixing 250 ml milk, 50 g cornflakes, 2 slices bread and 5 mg marmite in a stomacher containing 0.01 M HCl for 30 minutes, removing a 20 ml aliquot and measuring the phosphate content of a supernatant obtained from said aliquot, adding 2 g of said solid mixed metal compound to the contents of the

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stomacher, mixing for a further 30 minutes, taking another aliquot of food and
measuring the phosphate content of a supernatant obtained from this aliquot.

Claims 21-25 have been cancelled.

End of Appendix